

chain nodes :

12 16

ring nodes :

1 2 3 4 5 6 7 8 9 10 11 17 18 19 20 21 22

chain bonds :

3-12 5-10 7-16 9-19

ring bonds :

1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-11 8-9 9-10 10-11 17-18 17-22 18-19 19-20 20-21 21-22

exact/norm bonds :

3-12 5-10 7-8 7-11 7-16 8-9 9-10 9-19 10-11

normalized bonds :

1-2 1-6 2-3 3-4 4-5 5-6 17-18 17-22 18-19 19-20 20-21 21-22

isolated ring systems :

containing 1 : 7 :

G1:C,N

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom  
16:CLASS17:Atom 18:Atom 19:CLASS20:Atom 21:Atom 22:Atom

Generic attributes :

12:

Saturation : Unsaturated

10/522,970

=> (FILE 'HOME' ENTERED AT 13:18:23 ON 24 OCT 2006)

FILE 'REGISTRY' ENTERED AT 13:18:31 ON 24 OCT 2006

L1 STRUCTURE uploaded

L2 0 S L1 SAM

L3 43 S L1 FULL

FILE 'STNGUIDE' ENTERED AT 13:19:32 ON 24 OCT 2006

FILE 'REGISTRY' ENTERED AT 13:20:39 ON 24 OCT 2006

L4 STRUCTURE uploaded

L5 7 S L4 SAM

L6 88 S L4 FULL

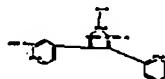
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L7 5 S L6

L8 1 S L7 AND PD<JULY 2003

file reg

=> Uploading C:\Program Files\Stnexp\Queries\b522970.str



chain nodes :

12 16

ring nodes :

1 2 3 4 5 6 7 8 9 10 11 17 18 19 20 21 22

chain bonds :

3-12 5-10 7-16 9-19

ring bonds :

1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-11 8-9 9-10 10-11 17-18 17-22 18-19 19-20 20 20-21 21-22

exact/norm bonds :

3-12 5-10 7-8 7-11 7-16 8-9 9-10 9-19 10-11

normalized bonds :

1-2 1-6 2-3 3-4 4-5 5-6 17-18 17-22 18-19 19-20 20-21 21-22

isolated ring systems :

containing 1 : 7 :

G1:C,N

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom  
11:Atom 12:Atom 16:CLASS 17:Atom 18:Atom 19:CLASS 20:Atom 21:Atom 22:Atom

Generic attributes :

12:

Saturation : Unsaturated

L4 STRUCTURE uploaded

=> dis 14

L4 HAS NO ANSWERS

L4 STR

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

Structure attributes must be viewed using STN Express query preparation.

=> s 14 sam  
L5 7 SEA SSS SAM L4=> s 14 full  
L6 88 SEA SSS FUL L4

=&gt; file caplus

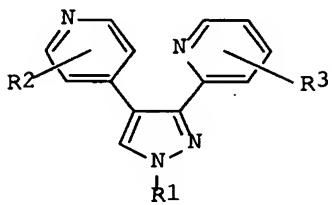
=> s 16  
L7 5 L6=> s 17 and pd<july 2003  
23677239 PD<JULY 2003  
(PD<20030700)  
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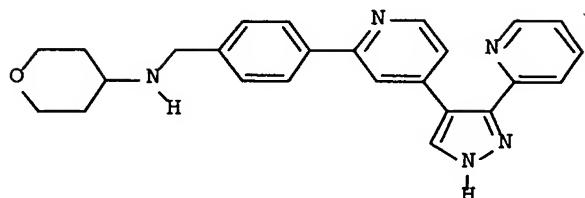
L8 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2002:658110 CAPLUS Full-text  
 DN 137:201305  
 TI Pyridinyl-substituted pyrazole derivatives useful against TGF- $\beta$   
 overexpression, and their preparation and use  
 IN Gellibert, Francoise Jeanne; Mathews, Neil  
 PA Glaxo Group Limited, UK  
 SO PCT Int. Appl., 62 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002066462	A1	20020829	WO 2002-EP938	20020130 <--
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EP	1355903	A1	20031029	EP 2002-719740	20020130
EP	1355903	B1	20050316		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP	2004521915	T2	20040722	JP 2002-565977	20020130
AT	291020	E	20050415	AT 2002-719740	20020130
ES	2237671	T3	20050801	ES 2002-2719740	20020130
US	2004087623	A1	20040506	US 2003-470856	20030731
PRAI	GB 2001-2661	A	20010202		

GB 2001-19424 A 20010809  
 WO 2002-EP938 W 20020130  
 OS MARPAT 137:201305  
 GI



I



II

AB Therapeutically active pyrazole derivs. of formula I are disclosed, as well as processes for their preparation, their use in therapy [particularly in the treatment or prophylaxis of disorders characterized by overexpression of transforming growth factor  $\beta$  (TGF- $\beta$ )], and pharmaceutical compns. for use in such therapy. In formula I, R1 is selected from H, C1-4 alkyl or CH2CONR4R5, where R4 is selected from H or C1-4 alkyl and R5 is C1-4 alkyl; R2 is selected from Ph, furanyl, or thienyl, wherein the Ph may be further substituted by one or more substituents, which may be the same or different, selected from halo (such as F, Cl, Br), cyano, CF3, OCF3, C1-4 alkyl, OR6, O(CH2)nXR6R7, O(CH2)nOR6, O(CH2)ncOR6, O(CH2)n-C2-6-alkenyl, O(CH2)n-C2-6-alkynyl, (CH2)nNR6R7, CONR6R7, NHCOR6, and NR6R7, where n is 1 to 6, and X is C, N, or S, and wherein the furanyl and thienyl may be further substituted by one or more substituents, which may be the same or different, selected from halo, cyano, CF3, OH, OCF3, C1-4 alkyl, and C1-4 alkoxy. Furthermore, R6 and R7 which may be the same or different, are selected from H, C1-6 alkyl, cycloalkyl, cycloalkyl-C1-6-alkyl, aryl, aryl-C1-6-alkyl, heteroaryl, heteroaryl-C1-6-alkyl, heterocyclyl, heterocyclyl-C1-6-alkyl, C1-4-alkoxy-C1-6-alkyl, hydroxy-C1-6-alkyl, (CH2)nNR8R9; or R6R7 together with the atom to which they are attached form a 3- to 7-membered saturated or unsatd. ring which may contain one or more heteroatoms selected from N, S, or O, and wherein the ring may be further substituted by one or more substituents selected from halo, cyano, CF3, OH, OCF3, C1-4 alkyl, C1-4 alkoxy and NR8R9; R8 and R9 which may be the same or different are selected from H or C1-6 alkyl, wherein the C1-6 alkyl may be further substituted by one or more substituents selected from halo, cyano, CF3, and OH; R3 is selected from H, halo, cyano, CF3, C1-4 alkyl, and C1-4 alkoxy. Salts and solvates of I are included as well. I are TGF- $\beta$  inhibitors which act at the TGF- $\beta$  type I (Alk5) receptor level, and thereby inhibit phosphorylation of the Smad-2 or Smad-3 proteins. Projected uses include treatment or prophylaxis of diseases such as fibrosis (especially liver or kidney), cancer development, abnormal bone function, inflammatory disorders, and scarring. The compds. are particularly suited to treatment of fibrosis and related conditions. Preps. of 47 compds.

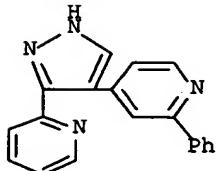
and various intermediates are given. For instance, 2-bromo-4-methylpyridine was deprotonated and condensed with Et picolinate to give 2-(2-bromopyridin-4-yl)-1-(pyridin-2-yl)ethanone. Cyclocondensation of this ketone with DMF di-Me acetal and hydrazine gave the corresponding pyrazole, which was protected by N-tritylation and arylated at bromine using 4-formylphenylboronic acid under Pd(0) catalysis. The resultant aldehyde was reductively aminated by 4-aminotetrahydropyran and NaBH(OAc)<sub>3</sub> to give title compound II. All 47 compds. I inhibited TGF- $\beta$  signaling in vitro with IC<sub>50</sub> values of 5  $\mu$ M or below, and inhibited the kinase Alk5 receptor (cloned, expressed in baculovirus/Sf9 cells) with IC<sub>50</sub> values of 1  $\mu$ M or less.

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

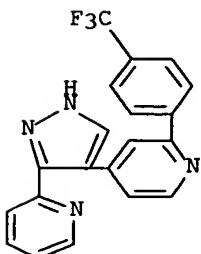
L8 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN  
 IT 452342-37-9P, 2-Phenyl-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-38-0P, 2-[4-(Trifluoromethyl)phenyl]-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-39-1P, 2-(4-Methoxyphenyl)-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-40-4P, 2-(4-Fluorophenyl)-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-41-5P, 2-(4-Chlorophenyl)-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-43-7P, 2-[4-(Trifluoromethoxy)phenyl]-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-44-8P, 2-(4-Methylphenyl)-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-45-9P, 2-(4-Ethylphenyl)-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-48-2P, 2-[4-[2-(Pyrrolidin-1-yl)ethoxy]phenyl]-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-50-6P, 3-[[4-[4-[3-(Pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]benzyl]amino]propanenitrile 452342-51-7P, 4-[4-[4-[3-(Pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]morpholine 452342-52-8P, 2-[4-[(1-Methyl-1H-imidazol-4-yl)methoxy]phenyl]-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-53-9P, 2-[4-[(1-Methyl-1H-imidazol-2-yl)methoxy]phenyl]-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-54-0P, 2-[4-[(3-Methyl-3H-imidazol-4-yl)methoxy]phenyl]-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-55-1P, 2-[4-[2-(1H-Imidazol-1-yl)ethoxy]phenyl]-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-56-2P, [4-[4-[3-(Pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]benzyl](tetrahydropyran-4-yl)amine 452342-57-3P, 4-[4-[4-[3-(Pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]benzyl]morpholine hydrochloride 452342-58-4P, (Pyridin-3-ylmethyl)[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]benzyl]amine 452342-59-5P, 2-(Piperidin-1-yl)-N-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]acetamide 452342-60-8P, 2-(Pyrrolidin-1-yl)-N-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]acetamide 452342-61-9P, 2-(Morpholin-4-yl)-N-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]acetamide 452342-62-0P, 2-(4-Methylpiperazin-1-yl)-N-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]acetamide 452342-63-1P, 3-(Piperidin-1-yl)-N-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]propionamide hydrochloride 452342-64-2P, 3-(Morpholin-4-yl)-N-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]propionamide 452342-65-3P, 3-(4-Methylpiperazin-1-yl)-N-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]propionamide 452342-67-5P, 4-[4-[3-(Pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]propionamide 452342-69-7P, N-[(tetrahydropyran-4-yl)benzamide 452342-71-1P, 1-Ethyl-4-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]piperazine 452342-73-3P, N-Methyl-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl](tetrahydropyran-4-yl)amine 452342-75-5P,

[[4-[4-[3-(Pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl](tetrahydropyran-4-yl)amine 452342-77-7P,  
 N-Methyl-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]benzyl](tetrahydropyran-4-yl)amine 452342-79-9P,  
 4-Methoxy-1-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]benzyl]piperidine 452342-81-3P, 1-[4-[4-[3-(Pyridin-2-yl)-1H-pyrazol-4-yl]benzyl]pyrrolidine 452342-83-5P,  
 1-Methyl-4-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]benzyl]piperazine 452342-85-7P, (1-Methylpiperidin-4-yl)[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]benzyl]amine 452342-87-9P, 1-Methyl-4-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]benzoyl]piperazine 452342-89-1P,  
 4-[4-[4-[3-(Pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]benzoyl]morpholine 452342-90-4P, 4-(Dimethylamino)-1-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]benzoyl]piperidine 452342-92-6P,  
 1-Methyl-4-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]piperazine 452342-93-7P, 4-[4-[4-[3-(Pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]benzyl]thiomorpholine 452342-94-8P,  
 Dimethyl[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]benzyl]amine 452342-95-9P, 4-[4-[3-(Pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]-N-(tetrahydropyran-4-ylmethyl)benzamide 452342-96-0P,  
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 N-(Cyclohexylmethyl)-4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]benzamide  
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (drug candidate)

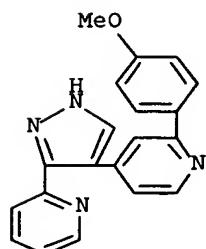
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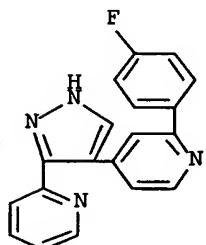
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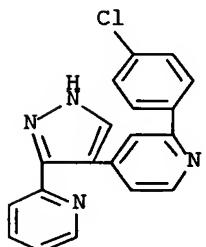
RN 452342-39-1 CAPLUS

CN Pyridine, 2-(4-methoxyphenyl)-4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]- (9CI)  
(CA INDEX NAME)

RN 452342-40-4 CAPLUS

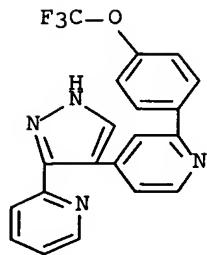
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RN 452342-41-5 CAPLUS

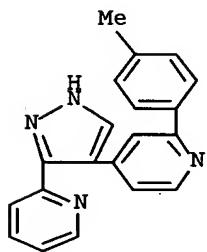
CN Pyridine, 2-(4-chlorophenyl)-4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]- (9CI)  
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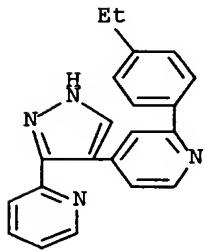
CN Pyridine, 4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-[4-(trifluoromethoxy)phenyl]- (9CI) (CA INDEX NAME)



RN 452342-44-8 CAPLUS

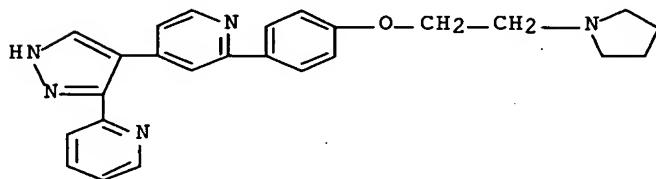
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RN 452342-45-9 CAPLUS

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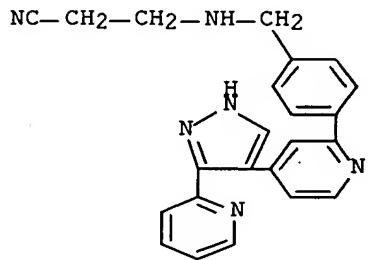
RN 452342-48-2 CAPLUS

CN Pyridine, 4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



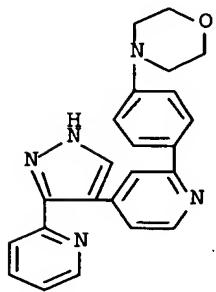
RN 452342-50-6 CAPLUS

CN Propanenitrile, 3-[[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]methyl]amino]- (9CI) (CA INDEX NAME)



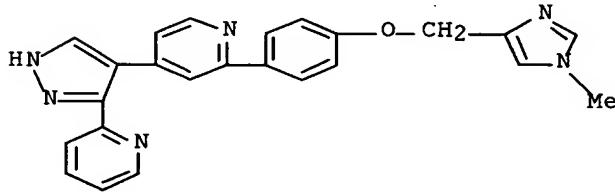
RN 452342-51-7 CAPLUS

CN Morpholine, 4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)



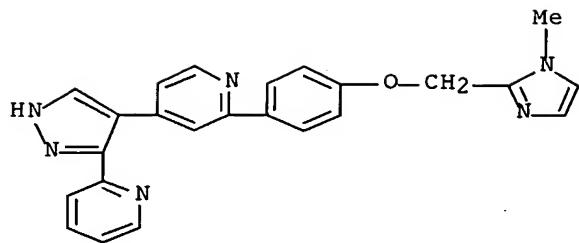
RN 452342-52-8 CAPLUS

CN Pyridine, 2-[4-[(1-methyl-1H-imidazol-4-yl)methoxy]phenyl]-4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]- (9CI) (CA INDEX NAME)



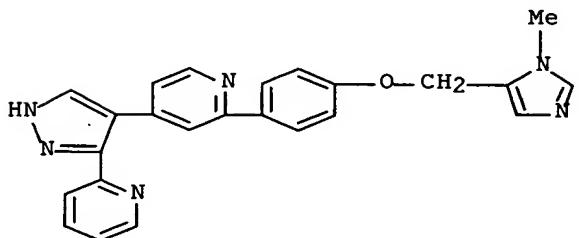
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CN Pyridine, 2-[4-[(1-methyl-1H-imidazol-2-yl)methoxy]phenyl]-4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]- (9CI) (CA INDEX NAME)



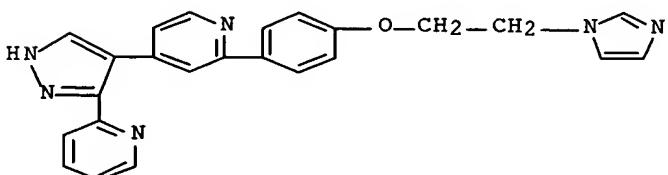
RN 452342-54-0 CAPLUS

CN Pyridine, 2-[4-[(1-methyl-1H-imidazol-5-yl)methoxy]phenyl]-4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]- (9CI) (CA INDEX NAME)



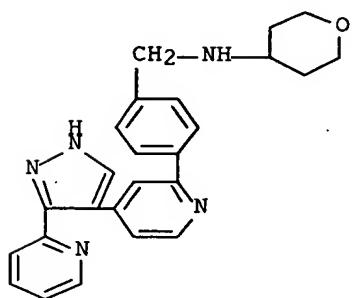
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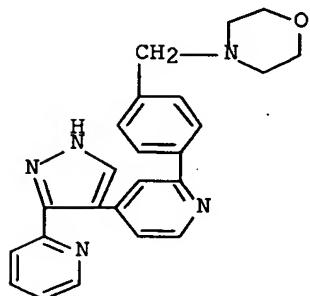
RN 452342-56-2 CAPLUS

CN 2H-Pyran-4-amine, tetrahydro-N-[[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]methyl- (9CI) (CA INDEX NAME)



RN 452342-57-3 CAPLUS

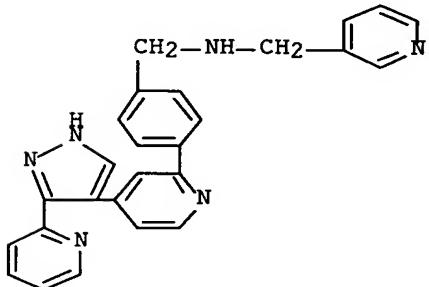
CN Morpholine, 4-[[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]methyl]-, hydrochloride (9CI) (CA INDEX NAME)



●x HCl

RN 452342-58-4 CAPLUS

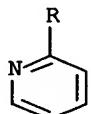
CN 3-Pyridinemethanamine, N-[[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



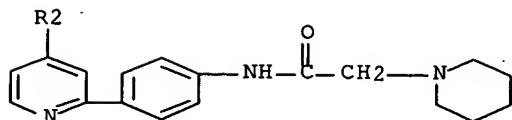
RN 452342-59-5 CAPLUS

CN 1-Piperidineacetamide, N-[[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

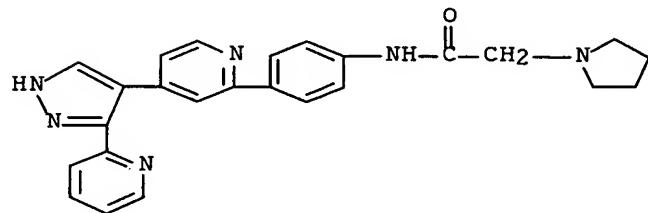


PAGE 2-A



RN 452342-60-8 CAPLUS

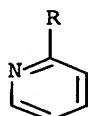
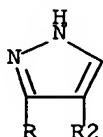
CN 1-Pyrrolidineacetamide, N-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)



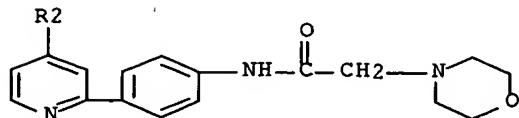
RN 452342-61-9 CAPLUS

CN 4-Morpholineacetamide, N-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



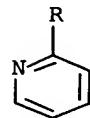
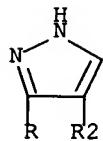
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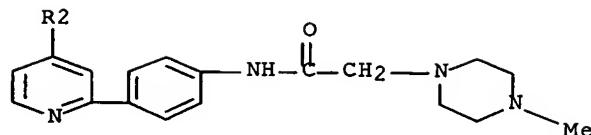
RN 452342-62-0 CAPLUS

CN 1-Piperazineacetamide, 4-methyl-N-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



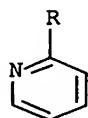
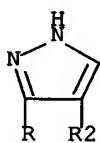
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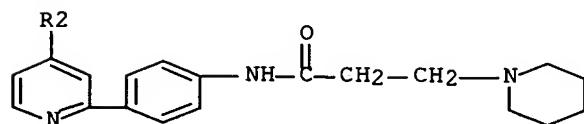
RN 452342-63-1 CAPLUS

CN 1-Piperidinepropanamide, N-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]-, hydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

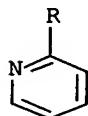
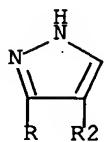


●x HCl

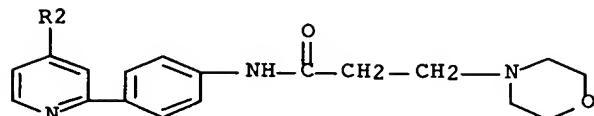
RN 452342-64-2 CAPLUS

CN 4-Morpholinepropanamide, N-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



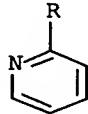
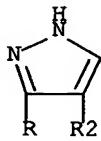
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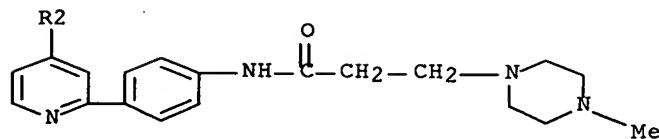
RN 452342-65-3 CAPLUS

CN 1-Piperazinepropanamide, 4-methyl-N-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



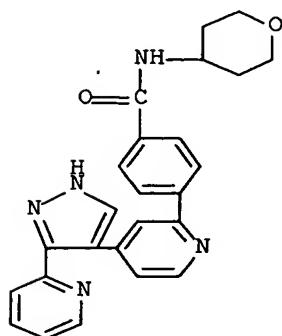
PAGE 2-A



RN 452342-67-5 CAPLUS

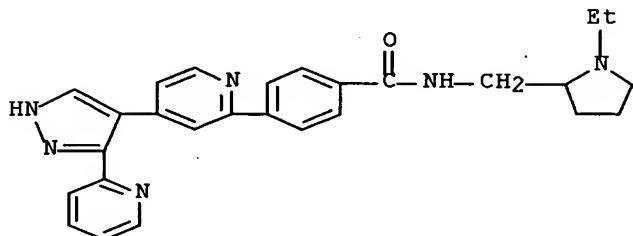
CN Benzamide, 4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]-N-

(tetrahydro-2H-pyran-4-yl) - (9CI) (CA INDEX NAME)



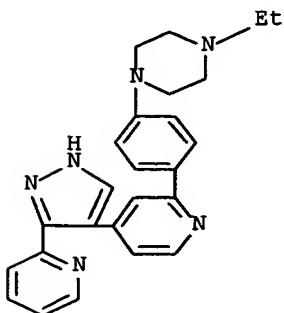
RN 452342-69-7 CAPLUS

CN Benzamide, N-[(1-ethyl-2-pyrrolidinyl)methyl]-4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]- (9CI) (CA INDEX NAME)



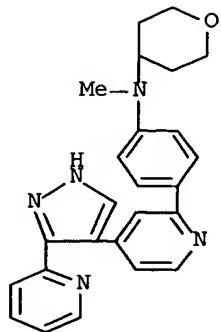
RN 452342-71-1 CAPLUS

CN Piperazine, 1-ethyl-4-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)



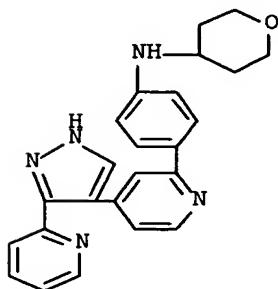
RN 452342-73-3 CAPLUS

CN 2H-Pyran-4-amine, tetrahydro-N-methyl-N-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)



RN 452342-75-5 CAPLUS

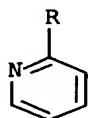
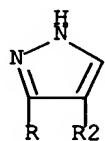
CN 2H-Pyran-4-amine, tetrahydro-N-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)

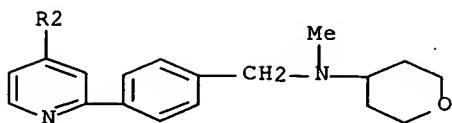


RN 452342-77-7 CAPLUS

CN 2H-Pyran-4-amine, tetrahydro-N-methyl-N-[[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

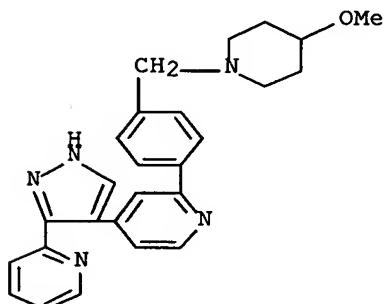
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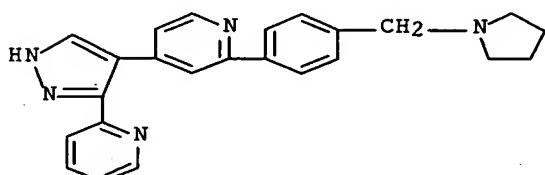
RN 452342-79-9 CAPLUS

CN Pyridine, 2-[4-[(4-methoxy-1-piperidinyl)methyl]phenyl]-4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]- (9CI) (CA INDEX NAME)



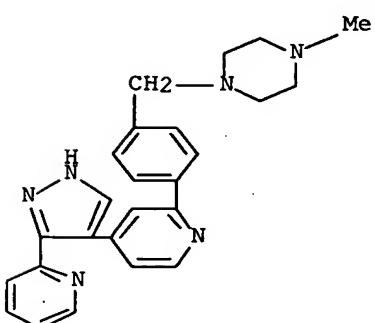
RN 452342-81-3 CAPLUS

CN Pyridine, 4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-[4-(1-pyrrolidinylmethyl)phenyl]- (9CI) (CA INDEX NAME)



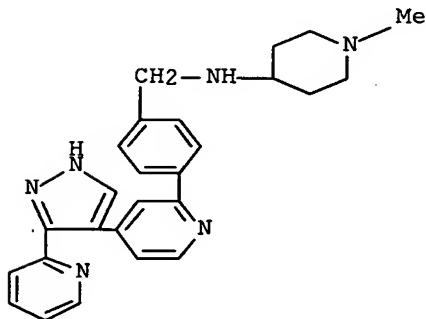
RN 452342-83-5 CAPLUS

CN Piperazine, 1-methyl-4-[[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



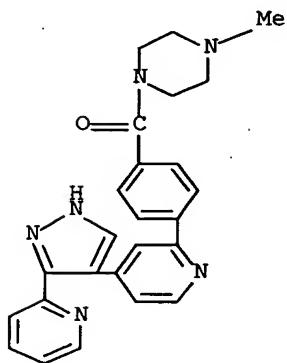
RN 452342-85-7 CAPLUS

CN 4-Piperidinamine, 1-methyl-N-[(4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl)methyl]- (9CI) (CA INDEX NAME)



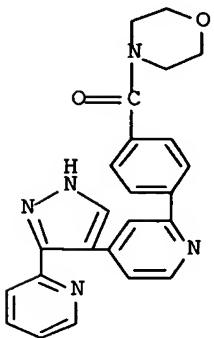
RN 452342-87-9 CAPLUS

CN Piperazine, 1-methyl-4-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]benzoyl]- (9CI) (CA INDEX NAME)



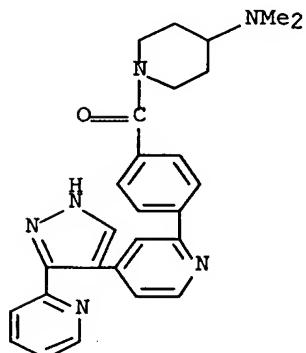
RN 452342-89-1 CAPLUS

CN Morpholine, 4-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]benzoyl]- (9CI) (CA INDEX NAME)



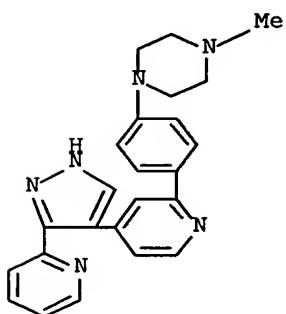
RN 452342-90-4 CAPLUS

CN 4-Piperidinamine, N,N-dimethyl-1-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]benzoyl]- (9CI) (CA INDEX NAME)



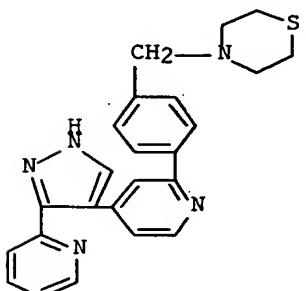
RN 452342-92-6 CAPLUS

CN Piperazine, 1-methyl-4-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)



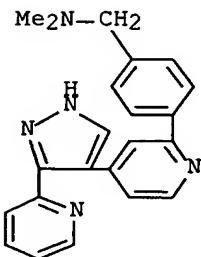
RN 452342-93-7 CAPLUS

CN Thiomorpholine, 4-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]methyl- (9CI) (CA INDEX NAME)



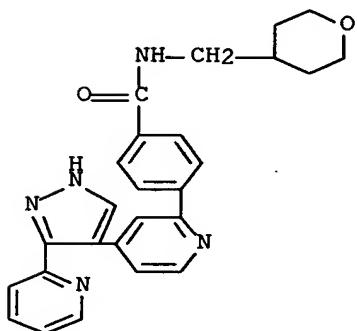
RN 452342-94-8 CAPLUS

CN Benzenemethanamine, N,N-dimethyl-4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]- (9CI) (CA INDEX NAME)



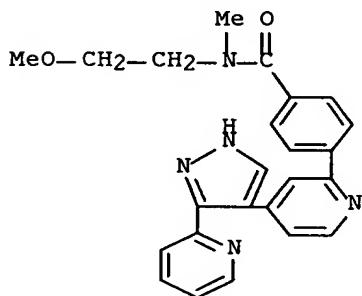
RN 452342-95-9 CAPLUS

CN Benzamide, 4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]-N-[(tetrahydro-2H-pyran-4-yl)methyl]- (9CI) (CA INDEX NAME)



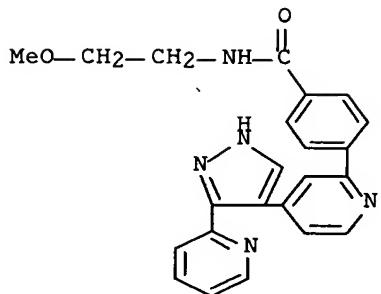
RN 452342-96-0 CAPLUS

CN Benzamide, N-(2-methoxyethyl)-N-methyl-4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]- (9CI) (CA INDEX NAME)



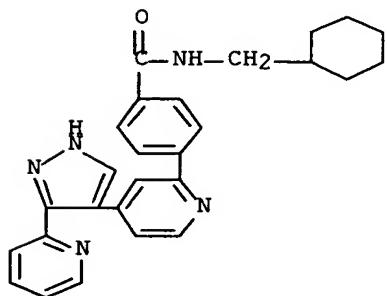
RN 452342-97-1 CAPLUS

CN Benzamide, N-(2-methoxyethyl)-4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]- (9CI) (CA INDEX NAME)



RN 452342-98-2 CAPLUS

CN Benzamide, N-(cyclohexylmethyl)-4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]- (9CI) (CA INDEX NAME)



=&gt; s 17 not 18

L9 4 L7 NOT L8

=&gt; dis 1-4 bib abs

L9 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN

AN 2006:237133 CAPLUS Full-text

DN 144:460293

TI Discovery of 4-[4-[3-(Pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]-N-(tetrahydro-2H-pyran-4-yl)benzamide (GW788388): A Potent, Selective, and Orally Active Transforming Growth Factor- $\beta$  Type I Receptor Inhibitor

AU Gellibert, Francoise; de Gouville, Anne-Charlotte; Woolven, James; Mathews, Neil; Nguyen, Van-Loc; Bertho-Ruault, Cecile; Patikis, Angela; Grygielko, Eugene T.; Laping, Nicholas J.; Huet, Stephane

CS Department of Medicinal Chemistry and Biology, GlaxoSmithKline, Les Ulis, 91951, Fr.

SO Journal of Medicinal Chemistry (2006), 49(7), 2210-2221

CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

DT Journal

LA English

OS CASREACT 144:460293

AB Inhibitors of transforming growth factor  $\beta$  (TGF- $\beta$ ) type I receptor (ALK5) offer a novel approach for the treatment of fibrotic diseases such as renal, hepatic, and pulmonary fibrosis. The optimization of a novel phenylpyridine

pyrazole series (1a) led to the identification of potent, selective, and orally active ALK5 inhibitors. The cellular potency and pharmacokinetics profiles of these derivs. were improved and several compds. presented antifibrotic activity when orally administered to rats in an acute liver model of dimethylnitrosamine- (DMN-) induced expression of collagen IAI mRNA, a major gene contributing to excessive extra cellular matrix deposit. One of the most potent ALK5 inhibitors identified in this chemical series, compound 13d (GW788388), reduced the expression of collagen IAI by 80% at a dose of 1 mg/kg twice a day (b.i.d.). This compound significantly reduced the expression of collagen IAI mRNA when administered orally at 10 mg/kg once a day (u.i.d.) in a model of puromycin aminonucleoside-induced renal fibrosis.

RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN  
AN 2005:420278 CAPLUS Full-text  
DN 143:126677  
TI Inhibition of TGF- $\beta$  signaling by an ALK5 inhibitor protects rats from dimethylnitrosamine-induced liver fibrosis  
AU de Gouville, Anne-Charlotte; Boullay, Valerie; Krysa, Gael; Pilot, Julia; Brusq, Jean-Marie; Loriole, Florence; Gauthier, Jean-Michel; Papworth, Stephen A.; Laroze, Alain; Gellibert, Francoise; Huet, Stephane  
CS Biology Department, GlaxoSmithKline, Les Ulis, 91951, Fr.  
SO British Journal of Pharmacology (2005), 145(2), 166-177  
CODEN: BJPCBM; ISSN: 0007-1188  
PB Nature Publishing Group  
DT Journal  
LA English  
AB Chronic liver disease is characterized by an exacerbated accumulation of matrix, causing progressive fibrosis, which may lead to cirrhosis. Transforming growth factor beta (TGF- $\beta$ ), a well-known profibrotic cytokine, transduces its signal through the ALK5 ser/thr kinase receptor, and increases transcription of different genes including PAI-1 and collagens. The identification of GW6604 (2-phenyl-4-(3-pyridin-2-yl-1H-pyrazol-4-yl)pyridine), an ALK5 inhibitor, allowed us to evaluate the therapeutic potential of inhibiting TGF- $\beta$  pathway in different models of liver disease. A cellular assay was used to identify GW6604 as a TGF- $\beta$  signaling pathway inhibitor. This ALK5 inhibitor was then tested in a model of liver hepatectomy in TGF- $\beta$ -overexpressing transgenic mice, in an acute model of liver disease and in a chronic model of dimethylnitrosamine (DMN)-induced liver fibrosis. In vitro, GW6604 inhibited autophosphorylation of ALK5 with an IC<sub>50</sub> of 140 nM and in a cellular assay inhibited TGF- $\beta$ -induced transcription of PAI-1 (IC<sub>50</sub>: 500 nM). In vivo, GW6604 (40 mg kg<sup>-1</sup> p.o.) increased liver regeneration in TGF- $\beta$ -overexpressing mice, which had undergone partial hepatectomy. In an acute model of liver disease, GW6604 reduced by 80% the expression of collagen IAI. In a chronic model of DMN-induced fibrosis where DMN was administered for 6 wk and GW6604 dosed for the last 3 wk (80 mg kg<sup>-1</sup> p.o., b.i.d.), mortality was prevented and DMN-induced elevations of mRNA encoding for collagen IAI, IA2, III, TIMP-1 and TGF- $\beta$  were reduced by 50-75%. Inhibition of matrix genes overexpression was accompanied by reduced matrix deposition and reduction in liver function deterioration, as assessed by bilirubin and liver enzyme levels. Our results suggest that inhibition of ALK5 could be an attractive new approach to treatment of liver fibrotic diseases by both preventing matrix deposition and promoting hepatocyte regeneration.

RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN

AN 2004:162684 CAPLUS Full-text

DN 140:199324

TI Preparation of (pyridyl)(phenylpyridyl)pyrazoles as inhibitors of the transforming growth factor  $\beta$ 

IN Gellibert, Francoise Jeanne

PA Smithkline Beecham Corporation, USA

SO PCT Int. Appl., 49 pp.

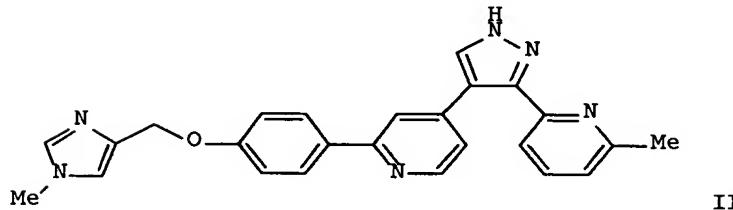
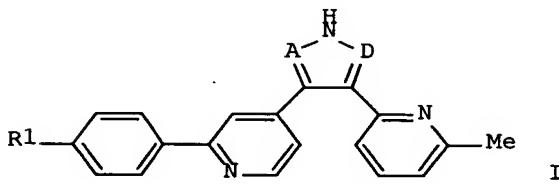
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004016606	A1	20040226	WO 2003-EP8449	20030729
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	AU 2003255333	A1	20040303	AU 2003-255333	20030729
	EP 1554268	A1	20050720	EP 2003-787752	20030729
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	JP 2005539026	T2	20051222	JP 2004-528450	20030729
	US 2006058329	A1	20060316	US 2005-522970	20050131
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	WO 2003-EP8449	W	20030729		
OS	MARPAT	140:199324			
GI					



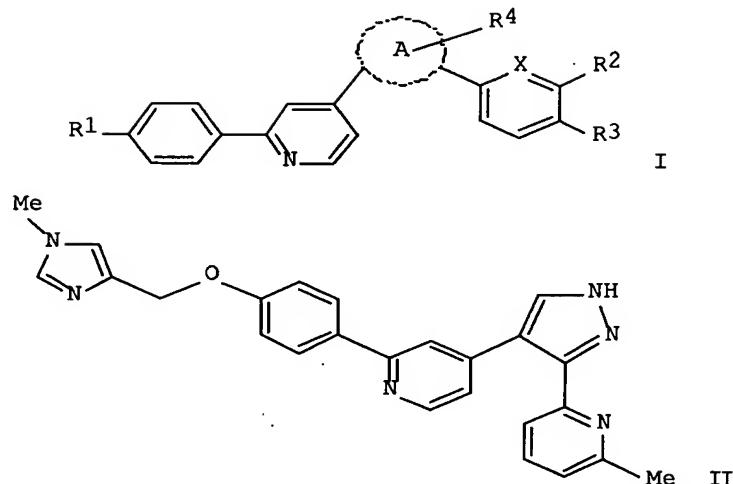
AB Title compds. I [wherein either A = CR<sub>2</sub> and D = N or A = N and D = CR<sub>2</sub>; R<sub>1</sub> = H, (perfluoro)alkyl, alkenyl, (perfluoro)alkoxy, halo, cyano, NR<sub>3</sub>R<sub>4</sub>, (CH<sub>2</sub>)<sub>n</sub>NR<sub>3</sub>R<sub>4</sub>, O(CH<sub>2</sub>)<sub>n</sub>OR<sub>5</sub>, O(CH<sub>2</sub>)<sub>n</sub>NR<sub>3</sub>R<sub>4</sub>, O(CH<sub>2</sub>)<sub>n</sub>-Het, CONR<sub>3</sub>R<sub>4</sub>, CO(CH<sub>2</sub>)<sub>n</sub>NR<sub>3</sub>R<sub>4</sub>, SO<sub>2</sub>R<sub>5</sub>, SO<sub>2</sub>NR<sub>3</sub>R<sub>4</sub>, NR<sub>3</sub>SO<sub>2</sub>R<sub>5</sub>, NR<sub>3</sub>COR<sub>5</sub>, NR<sub>3</sub>CO(CH<sub>2</sub>)<sub>n</sub>NR<sub>3</sub>R<sub>4</sub>, Het, or O(CH<sub>2</sub>)<sub>n</sub>CONR<sub>3</sub>R<sub>4</sub>; R<sub>2</sub> = H or alkyl; R<sub>3</sub> and R<sub>4</sub> = independently H, (alkoxy)alkyl, or Het; or NR<sub>3</sub>R<sub>4</sub>]

= (un)substituted heterocyclyl; R5 = H or alkyl; Het = (un)substituted 5- or 6-membered C-linked heterocyclyl; n = 1-4; or pharmaceutically acceptable salts, solvates, or derivs. thereof] were prepared as inhibitors of the transforming growth factor  $\beta$  (TGF- $\beta$ ) signaling pathway, in particular, the phosphorylation of smad2 or smad3 by the TGF- $\beta$  type I or activin-like kinase (ALK) 5 receptor. For example, reaction of 4-[4-[3-(6-methylpyridin-2-yl)-1-trityl-1H-pyrazol-4-yl]pyridin-2-yl]phenol with 1-methyl-4-chloromethylimidazole•HCl (preparation of starting materials given) in the presence of NaH in CH<sub>2</sub>Cl<sub>2</sub> provided the trityl intermediate, which was deprotected using HCl in MeOH to give II (37%). The latter inhibited TGF- $\beta$  signaling in HepG2 cells stably transfected with the PAI-1 promotor linked to a luciferase reporter gene with an IC<sub>50</sub> value of 34 nM. II also modulated ALK5 receptor activity with an IC<sub>50</sub> value of 5 nM. Thus, I and their pharmaceutical compns. are useful for the treatment of disorders mediated by the ALK5 receptor, such as kidney fibrosis (no data).

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN  
AN 2004:120851 CAPLUS Full-text  
DN 140:181331  
TI Preparation of 2-phenylpyridin-4-yl heterocycles as selective activin-like kinase-5 inhibitors useful against fibrosis and other disorders  
IN Dodic, Nerina; Gellibert, Francoise Jeanne  
PA Smithkline Beecham Corporation, USA  
SO PCT Int. Appl., 119 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004013135	A1	20040212	WO 2003-EP8496	20030729
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2003260345	A1	20040223	AU 2003-260345	20030729
	EP 1539748	A1	20050615	EP 2003-766385	20030729
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	JP 2005539000	T2	20051222	JP 2004-525405	20030729
	US 2005245520	A1	20051103	US 2005-522969	20050131
PRAI	GB 2002-17751	A	20020731		
	GB 2003-14698	A	20030624		
	WO 2003-EP8496	W	20030729		
OS	MARPAT 140:181331				
GI					



AB This invention relates to novel 2-phenylpyridin-4-yl heterocycles (shown as I; variables defined below; e.g. II) that are inhibitors of the transforming growth factor, ('TGF')- $\beta$  signaling pathway, in particular, the phosphorylation of Smad-2 or Smad-3 by the TGF- $\beta$  type I or activin-like kinase ('ALK')-5 receptor, methods for their preparation and their use in medicine, specifically in the treatment and prevention of a disease state mediated by this pathway, e.g. fibrosis (no data). All examples of I show ALK-5 receptor modulator activity (having IC<sub>50</sub> values at 0.4-275 nM) and TGF- $\beta$  cellular activity (having IC<sub>50</sub> values at 0.001-10  $\mu$ M). 4-[4-[4-[2-tert-Butyl-5-(6-methylpyridin-2-yl)-1H-imidazol-4-yl]pyridin-2-yl]phenyl]morpholine showed an ALK-5 receptor modulator activity of 34 nM and TGF- $\beta$  cellular activity of 183 nM. N-(tetrahydropyran-4-yl)-4-[4-[2-isopropyl-5-(6-methylpyridin-2-yl)-1H-imidazol-4-yl]pyridin-2-yl]benzamide showed an ALK-5 receptor modulator activity of 25 nM and TGF- $\beta$  cellular activity of <14 nM. Although the methods of preparation are not claimed, >150 example preps. of I and apprx. 130 example preps. of intermediates are included. For example, II was prepared in 37% yield by reacting 4-[4-[3-(6-methylpyridin-2-yl)-1-trityl-1H-pyrazol-4-yl]pyridin-2-yl]phenol and NaH in DMF with 1-methyl-4-hydroxymethylimidazole followed by removal of the trityl group using HCl in MeOH; details are also given for preparation of the reactants. For I: A is furan, dioxolane, thiophene, pyrrole, imidazole, pyrrolidine, pyran, pyridine, pyrimidine, morpholine, piperidine, oxazole, isoxazole, oxazoline, oxazolidine, thiazole, isothiazole, thiadiazole, benzofuran, indole, isoindole, indazole, imidazopyridine, quinazoline, quinoline, isoquinoline, pyrazole or triazole; X is N or CH; R1 is H, C1-6alkyl, C1-6alkenyl, C1-6alkoxy, halo, cyano, perfluoro C1-6alkyl, perfluoroC1-6alkoxy, -NR<sub>5</sub>R<sub>6</sub>, -(CH<sub>2</sub>)<sub>n</sub>NR<sub>5</sub>R<sub>6</sub>, -O(CH<sub>2</sub>)<sub>n</sub>OR<sub>7</sub>, -O(CH<sub>2</sub>)<sub>n</sub>Het, -O(CH<sub>2</sub>)<sub>n</sub>NR<sub>5</sub>R<sub>6</sub>, -CONR<sub>5</sub>R<sub>6</sub>, -CO(CH<sub>2</sub>)<sub>n</sub>NR<sub>5</sub>R<sub>6</sub>, -SO<sub>2</sub>R<sub>7</sub>, -SO<sub>2</sub>NR<sub>5</sub>R<sub>6</sub>, -NR<sub>5</sub>SO<sub>2</sub>R<sub>7</sub>, -NR<sub>5</sub>COR<sub>7</sub>, -O(CH<sub>2</sub>)<sub>n</sub>CONR<sub>5</sub>R<sub>6</sub>, -NR<sub>5</sub>CO(CH<sub>2</sub>)<sub>n</sub>NR<sub>5</sub>R<sub>6</sub> or -C(O)R<sub>7</sub>; R2 is H, C1-6alkyl, halo, cyano or perfluoroC1-6alkyl; R3 is H or halo; R4 is H, halo, Ph, C1-6alkyl or -NR<sub>5</sub>R<sub>6</sub>; addnl. details including provisos are given in the claims.

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COST IN U.S. DOLLARS

SINCE FILE  
ENTRY      TOTAL  
SESSION

10/522,970

FULL ESTIMATED COST	18.94	372.59
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
CA SUBSCRIBER PRICE	ENTRY	SESSION
	-3.75	-3.75

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